

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VEREGEN safely and effectively. See full prescribing information for VEREGEN.

VEREGEN (sinecatechins) ointment for topical use
Initial U.S. Approval: 2006

INDICATIONS AND USAGE

Veregen[®] is a topical ointment indicated for the treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older (1.1).

Limitations of Use: Safety and effectiveness of Veregen[®] have not been established in immunosuppressed patients, in treatment of external genital and perianal warts beyond 16-weeks, or for multiple treatment courses (1.2).

DOSAGE AND ADMINISTRATION

- Veregen[®] is to be applied three times per day to all external genital and perianal warts (2.1).
- Apply about an 0.5 cm strand of ointment to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts (2.1).
- Veregen[®] is not for ophthalmic, oral, intravaginal, or intra-anal use (2.1).

DOSAGE FORMS AND STRENGTHS

- Ointment, 15% (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Veregen[®] should not be used to treat urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease (5).
- Use of Veregen[®] on open wounds should be avoided (5).
- Avoid exposure of Veregen[®] treated areas to sun/UV-light as Veregen[®] has not been tested under these circumstances (5).

ADVERSE REACTIONS

Most common adverse reactions are local skin and application site reactions including (incidence \geq 20%) erythema, pruritis, burning, pain/discomfort, erosion/ulceration, edema, induration, and rash vesicular (6).

To report SUSPECTED ADVERSE REACTIONS, contact Bradley Pharmaceuticals, Inc. at 1-800-929-9300 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 10/2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

Veregen[®] is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

1.2 Limitations of Use

The safety and effectiveness of Veregen[®] have not been established for treatment beyond 16-weeks or for multiple treatment courses. The safety and effectiveness of Veregen[®] in immunosuppressed patients have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Veregen[®] is to be applied three times per day to all external genital and perianal warts.

Apply about an 0.5 cm strand of the Veregen[®] to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts. Patients should wash their hands before and after application of Veregen[®].

It is not necessary to wash off the ointment from the treated area prior to the next application.

Veregen[®] is not for ophthalmic, oral, intravaginal, or intra-anal use.

2.2 Treatment Period

Treatment with Veregen[®] should be continued until complete clearance of all warts, however no longer than 16 weeks.

Local skin reactions (e.g. erythema) at the treatment site are frequent. Nevertheless, treatment should be continued when the severity of the local skin reaction is acceptable.

3 DOSAGE FORMS AND STRENGTHS

Veregen[®] is a brown ointment and is supplied in aluminum tubes containing 15 grams (NDC # 10337-450-15) or 30 grams (NDC # 10337-450-03) of ointment per tube.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

Veregen[®] has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions.

Use of Veregen[®] on open wounds should be avoided.

Patients should be advised to avoid exposure of the genital and perianal area to sun/UV-light as Veregen[®] has not been tested under these circumstances.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Phase 3 clinical trials, a total of 397 subjects received Veregen[®] three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Serious local adverse events of pain and inflammation were reported in two subjects (0.5%), both women.

In clinical trials, the incidence of patients with local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simplex, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

Local and regional reactions (including adenopathy) occurring at >1% in the treated groups are presented in Table 1.

Table 1: Local and Regional Adverse Reactions During Treatment (% Subjects)

	Veregen [®] (N = 397)	Vehicle (N = 207)
Erythema	70	32
Pruritus	69	45
Burning	67	31

Pain/discomfort	56	14
Erosion/Ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6
Regional Lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

A total of 266/397 (67%) of subjects in the Veregen[®] group had either a moderate or a severe reaction that was considered probably related to the drug, of which 120 (30%) subjects had a severe reaction. Severe reactions occurred in 37% (71/192) of women and in 24% (49/205) of men. The percentage of subjects with at least one severe, related adverse event was 26% (86/328) for subjects with genital warts only, 42% (19/45) in subjects with both genital and perianal warts and 48% (11/23) of subjects with perianal warts only.

Phimosis occurred in 3% of uncircumcised male subjects (5/174) treated with Veregen[®] and in 1% (1/99) in vehicle.

The maximum mean severity of erythema, erosion, edema, and induration was observed by week 2 of treatment.

Less common local adverse events included urethritis, perianal infection, pigmentation changes, dryness, eczema, hyperesthesia, necrosis, papules, and discoloration. Other less common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash, and staphylococemia.

In a dermal sensitization study of Veregen[®] in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well controlled studies in pregnant women. Veregen[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The Maximum Recommended Human Dose (MRHD) of Veregen[®] was set at three times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg sinecatechins for the animal multiple of human exposure calculations presented in this labelling. Dose multiples were calculated based on the human equivalent dose (HED).

Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of sinecatechins during the period of organogenesis (gestational Days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of sinecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study.

A combined fertility / embryo-fetal development study using daily vaginal administration of Veregen[®] to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of Veregen[®] at doses of 0.05, 0.10 and 0.15 mL/rat/day from Day 6 of gestation through parturition and lactation. The high and intermediate dose levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F₀ dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction and fertility at any dose tested.

8.3 Nursing Mothers

It is not known whether topically applied Veregen[®] is excreted in breast milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

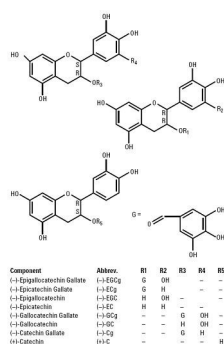
Seven patients (1.4%), older than 65 years of age were treated with Veregen[®] in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Veregen[®] (sin catechins) Ointment, 15% is a botanical drug product for topical use. The drug substance in Veregen[®] is sin catechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* (L.) O Kuntze, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg), and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

General Structure of Catechins



Each gram of the ointment contains 150 mg of sin catechins in a water free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mode of action of Veregen[®] involved in the clearance of genital and perianal warts is unknown. In vitro, sin catechins had anti-oxidative activity; the clinical significance of this finding is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of Veregen[®] is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of topically applied Veregen[®] has not been sufficiently characterized at this time. However, data suggest that systemic exposure to catechins after repeated topical application of Veregen[®] is likely to be less than observed after a single oral intake of 400 mL green tea.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral (gavage) carcinogenicity study, sin catechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD; [see Use in Specific Populations (8.1)]). Treatment with sin catechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Veregen[®] has not been evaluated in a dermal carcinogenicity study.

Sin catechins was negative in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay.

Daily vaginal administration of Veregen[®] to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

14 CLINICAL STUDIES

Two randomized, double-blind, vehicle-controlled studies were performed to investigate the safety and efficacy of Veregen[®] in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The subjects applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment). Over both studies the median baseline wart area was 51 mm² (range 12 to 585 mm²), and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16, presented in Tables 2 and 3 for all randomized subjects dispensed medication.

Table 2: Efficacy by Region

	Complete Clearance
All Countries (includes the United States)	
Veregen [®] 15% (N = 397)	213 (53.6%)
Vehicle (N = 207)	73 (35.3%)
United States	
Veregen [®] 15% (N = 21)	5 (23.8%)
Vehicle (N = 9)	0 (0.0%)

Table 3: Efficacy by Gender

	Complete Clearance
Males	
Veregen [®] 15% (N = 205)	97 (47.3%)
Vehicle (N = 118)	34 (28.8%)
Females	
Veregen [®] 15% (N = 192)	116 (60.4%)
Vehicle (N = 89)	39 (43.8%)

Median time to complete wart clearance was 16 weeks and 10 weeks, respectively, in the two phase 3 clinical trials.

The rate of recurrence of external genital and perianal warts 12 weeks after completion of treatment in subjects with complete clearance is 6.8% (14/206) for those treated with Veregen[®] and 5.8% (4/69) for those treated with vehicle.

16 HOW SUPPLIED/STORAGE AND HANDLING

Veregen[®] is a brown ointment and is supplied in aluminium tubes containing 15 grams (NDC # 10337-450-15) or 30 grams (NDC # 10337-450-03) of ointment per tube.

Prior to dispensing to the patient, store refrigerated 2# to 8# (36# to 46#). After dispensing, store refrigerated or up to 25# (77#). Do not freeze.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.2)

17.1 Instructions for Use

Patients using Veregen[®] should receive the following information and instructions:

- This medication is only to be used as directed by a physician. It is for external use only. Eye contact should be avoided as well as application into the vagina or anus.
- It is not necessary to wash off Veregen[®] prior to the next application. When the treatment area is washed or a bath is taken, the ointment should be applied afterwards.
- It is common for patients to experience local skin reactions such as erythema, erosion, edema, itching, and burning at the site of application. Severe skin reactions can occur and should be promptly reported to the healthcare provider. Should severe local skin reaction occur, the ointment should be removed by washing the treatment area with mild soap and water, and further doses withheld.

- Sexual (genital, anal or oral) contact should be avoided while the ointment is on the skin, or the ointment should be washed off prior to these activities. Veregen[®] may weaken condoms and vaginal diaphragms. Therefore, the use in combination with Veregen[®] is not recommended.
- Female patients using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental application of the ointment into the vagina must be avoided.
- Veregen[®] may stain clothing and bedding.
- Veregen[®] is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16-week treatment period, these should also be treated with Veregen[®].
- The effect of Veregen[®] on the transmission of genital/perianal warts is unknown.
- Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as Veregen[®] has not been tested under these circumstances.
- The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
- Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION

Veregen[®] (sinecatechins) Ointment, 15% Rx Only

Read this leaflet carefully before you start using Veregen[®] Ointment, 15% and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. If you have any questions about Veregen[®] Ointment, 15% or your condition ask your doctor or pharmacist. Only your doctor can prescribe Veregen[®] and determine if it is right for you.

What is Veregen[®] Ointment, 15%?

Veregen[®] Ointment, 15% is a medicine for skin use only (topical) for the treatment of warts on the outside of the genitals and around the outside of the anus. It is not a treatment for warts in the vagina, cervix, or inside the anus. Your doctor may recommend examination and screening tests (such as a Pap smear) to evaluate these areas.

Who should not use Veregen[®] Ointment, 15%?

Do not use Veregen[®] Ointment, 15% if you **are allergic** to an ingredient in Veregen[®] Ointment, 15%. **The list of ingredients is at the end of this leaflet.**

What should I tell my doctor before using Veregen[®] Ointment, 15%?

Tell your doctor about all your health conditions and all the medicines you take including prescription, over-the-counter medicine, vitamins, supplements, and herbals. Be sure to tell your doctor if you are:

- **pregnant or planning to become pregnant**, as it is not known if Veregen[®] Ointment, 15% can harm your unborn baby. Your doctor will determine whether the benefit outweighs the risk.
- **breastfeeding**, as it is not known if Veregen[®] Ointment, 15% can pass into your milk and if it can harm your baby.
- **using any other type of skin product or have open wounds on the area to be treated.** Veregen[®] Ointment, 15% should not be used until your skin has healed from other treatments applied to the same area.
- **immunocompromised.** This means that your immune system cannot fight infections as well as it should.

How should I use Veregen[®] Ointment, 15%?

- Use Veregen[®] Ointment, 15% only on the area affected **exactly** as prescribed by your doctor.

- **Wash your hands before and after application of Veregen[®] Ointment, 15%.** A small amount of the ointment should be applied to all warts using your finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts as directed by your doctor.
- **Apply Veregen[®] Ointment, 15% three times per day --- in the morning, at noontime and in the evening.**
- Do not wash off the ointment from the treated area before the next application. When you wash the treatment area or bathe, apply the ointment afterwards.
- Treatment with Veregen[®] Ointment, 15% should be continued until complete clearance of all warts, however **no longer than 16 weeks**. If your warts do not go away, or if they come back after treatment call your doctor.
- Veregen[®] Ointment, 15% is not a cure for warts on your genitals or around your anus with certainty. New warts may develop during or after treatment, and may need treatment.

What should I avoid while using Veregen[®] Ointment, 15%?

- Do not apply Veregen[®] Ointment, 15% on open wounds or into the vagina or into the anus.
- Genital warts are a sexually transmitted disease, and you may infect your partner.
- Avoid sexual contact (genital, anal or oral) when Veregen[®] Ointment, 15% is on your genital or perianal skin. If you do choose to have sexual contact, you must wash off the ointment carefully before having protected sexual contact as the ointment may weaken condoms and vaginal diaphragms. Talk to your doctor about safe sex practices.
- Avoid contact with your eyes, nostrils and mouth while ointment is on your finger(s).
- Women using tampons: insert the tampon before applying the ointment. If you need to change your tampon while the ointment is on your skin, avoid getting the ointment into the vagina.
- Uncircumcised men treating warts under the foreskin should retract the foreskin and clean the area daily.
- Do not expose the genital area treated with Veregen[®] Ointment, 15% to sunlight, sunlamps or tanning beds.
- Do not cover the treated area. Loose-fitting undergarments can be worn after applying Veregen[®] Ointment, 15%.
- Veregen[®] Ointment, 15% may stain your light colored clothes and bedding. It is recommended to wear darker colored undergarments while using Veregen[®] Ointment, 15%.

What are the possible side effects of Veregen[®] Ointment, 15%?

The most common side effects with Veregen[®] Ointment, 15% are local skin and application site reactions including:

- redness
- swelling
- sores or blisters
- burning
- itching
- pain

Many patients experience itching, reddening or swelling on or around the application site during the course of treatment. Some of these side effects could be a sign of an allergic reaction. If you experience open sores or other severe reactions at the locations you applied Veregen[®] Ointment, 15%, stop treatment and call your doctor right away.

You may experience other side effects of Veregen[®] Ointment, 15%, which are not mentioned here. Ask your doctor or pharmacist for more information.

Patients should be aware that new warts may develop during treatment as Veregen[®] Ointment, 15% is not a cure.

How should I store Veregen[®] Ointment, 15%?

- Store Veregen[®] Ointment, 15% refrigerated or up to 77°F (25 °C).
- Make sure the cap on the tube is tightly closed.
- Do not freeze.
- Safely throw away Veregen[®] Ointment, 15% tubes that are out of date or are empty.

Keep Veregen[®] Ointment, 15% and all medicines out of the reach of children.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Veregen[®] Ointment, 15% for a condition for which it was not prescribed. Do not give Veregen[®] Ointment, 15% to other people, even if they have the same symptoms you have. It may harm them. Do not use Veregen[®] Ointment, 15% after the expiration date on the tube. This leaflet summarizes the most important information about Veregen[®] Ointment, 15%. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Veregen[®] Ointment, 15% that is written for the doctor.

What are the ingredients in Veregen[®] Ointment, 15%?**Active ingredient:**

A defined green tea extract named sinecatechins.

Inactive ingredients:

Isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Veregen[®] is a trademark of MediGene AG, D-82152 Planegg/Martinsried, Germany.

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